Principles of Clinical Pharmacology

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Noncompartmental versus Compartmental Approaches to Pharmacokinetic Data Analysis

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Questions asked

* What does the body do to the drug?

  Pharmacokinetics

* What does the drug do to the body?

  Pharmacodynamics

* What is the effect of the drug on the body?

  Disease progression and management

* What is the variability in the population?

  Population pharmacokinetics

What is needed?

* A means by which to communicate the answers to the previous questions among individuals with diverse backgrounds
* The answer: **pharmacokinetic parameters**

Pharmacokinetic parameters

* Definition of pharmacokinetic parameters
* Formulas for the pharmacokinetic parameters
* Methods to estimate the parameters from the formulas using data

Pharmacokinetic parameters

* Descriptive or observational
* Quantitative (requiring a formula and a means to estimate using the formula)

Quantitative parameters

* Formula reflective the definition
* Data
* Estimation methods

Models for estimation

* Noncompartmental
* Compartmental

Goals of this lecture

* Description of the quantitative parameters
* Underlying assumptions of noncompartmental and compartmental models
* Parameter estimation methods
* What to expect from the results

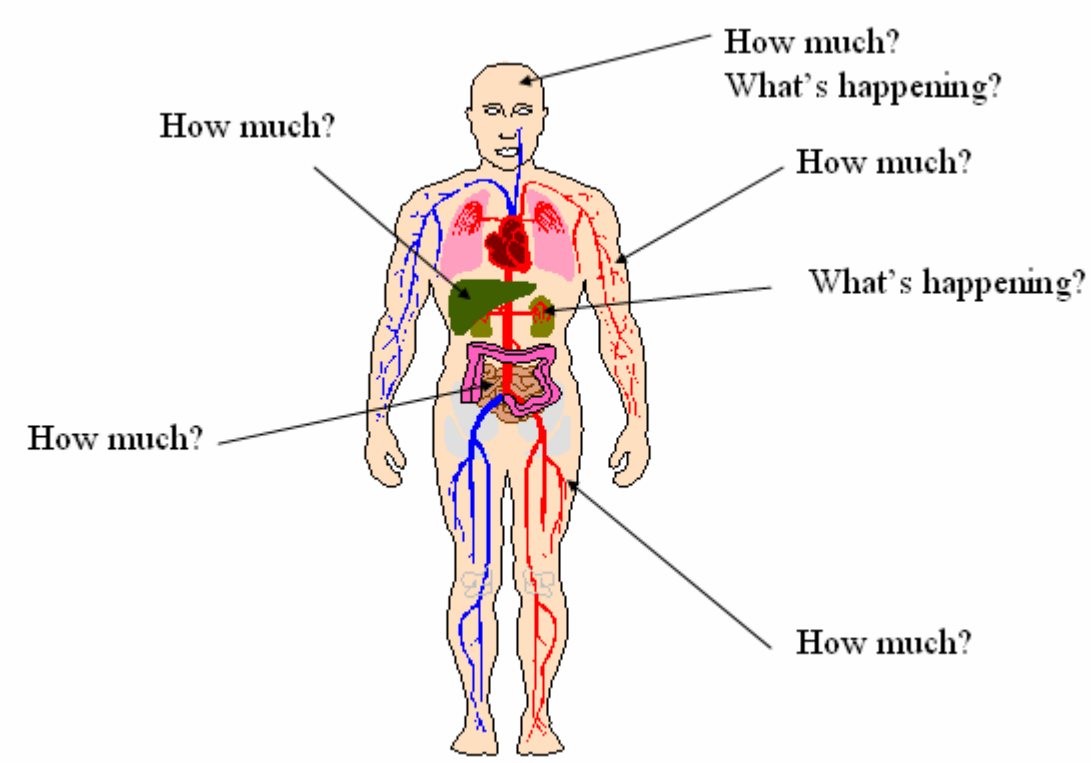
Goals of this lecture

* Not to conclude that one method is better than another
* What are the assumptions, and how can these affect the conclusions
* Make an intelligent choice of methods depending upon what information is required from the data

A drug in the body: constantly undergoing change

* Absorption
* Transport in the circulation
* Transport across membranes
* Biochemical transformation
* Elimination

A drug in the body: constantly undergoing change



Kinetics

The temporal and spatial distribution of a substance in a system.

Pharmacokinetics

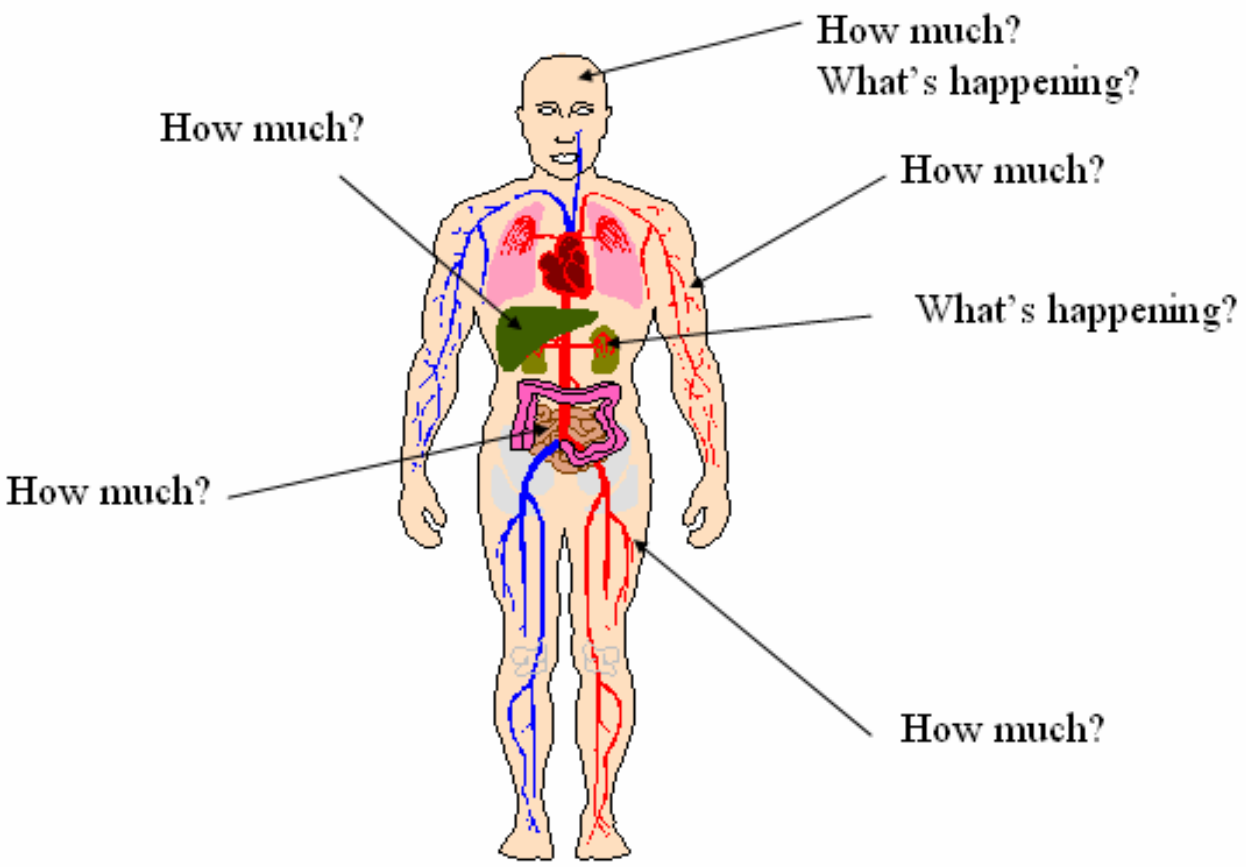
The temporal and spatial distribution of a drug (or drugs) in a system.

Definition of kinetics: consequences

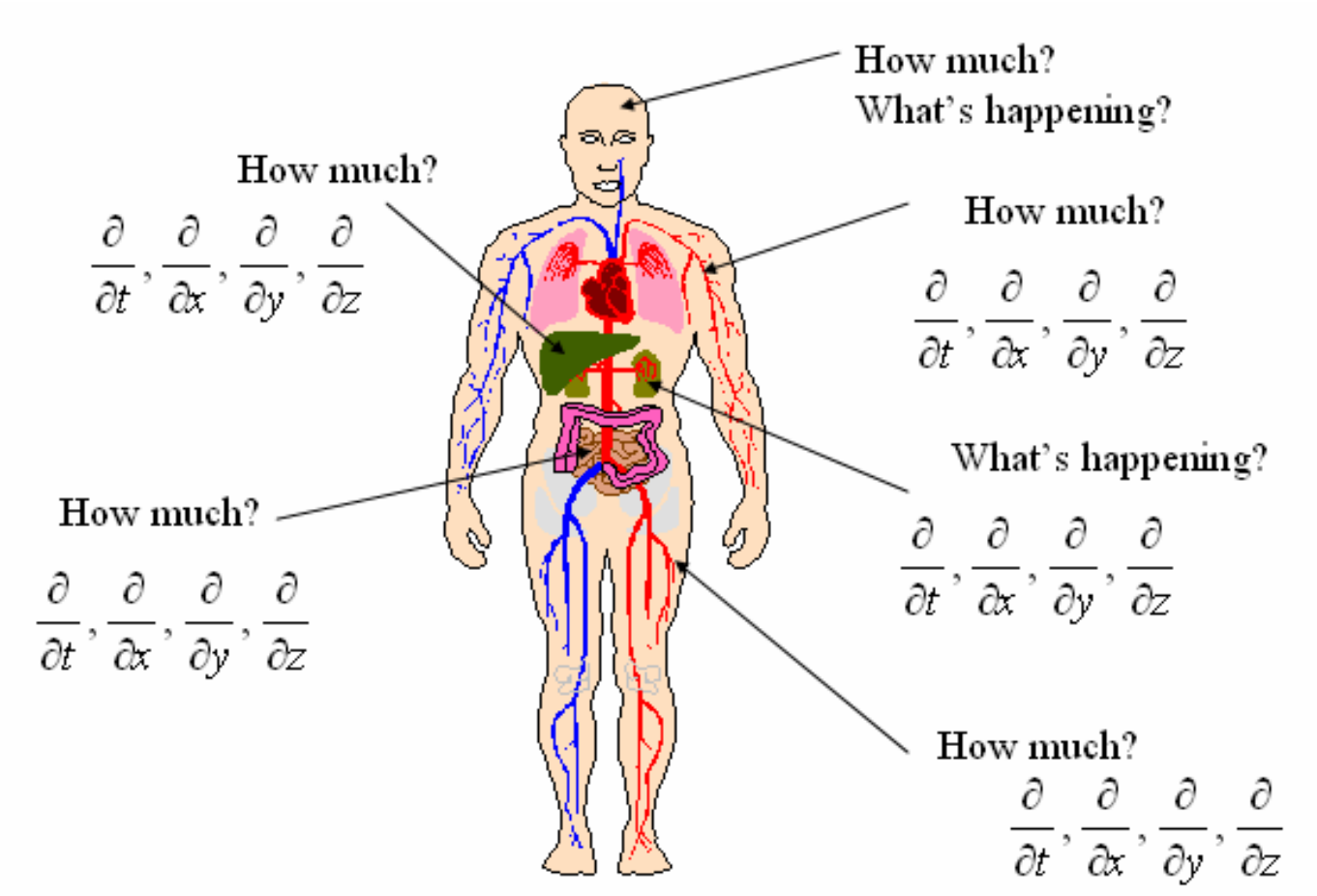
* Spatial: *Where* in the system
* Temporal: *When* in the system
* If (x,y,z) are spatial coordinates and c=c(s,t) is the measurement of a substance at a specific s, then the rate of change of the measurements depends upon s and t:

$$\frac{\partial c(\vec{s},t)}{\partial x}, \quad \frac{\partial c(\vec{s},t)}{\partial y}, \quad \frac{\partial c(\vec{s},t)}{\partial z}, \quad \frac{\partial c(\vec{s},t)}{\partial t}$$

A drug in the body: constantly undergoing change



A drug in the body: constantly undergoing change



Using partial derivatives

* Requires a knowledge of physical chemistry, irreversible thermodynamics and circulatory dynamics.
* Difficult to solve.
* Difficult to design an experiment to estimate parameter values.
* While desirable, normally not practical.
* Question: What can one do?

Resolving the problem

* Reducing the system to a finite number of components
* Lumping processes together based upon time, location or a combination of the two
* Space is not taken directly into account

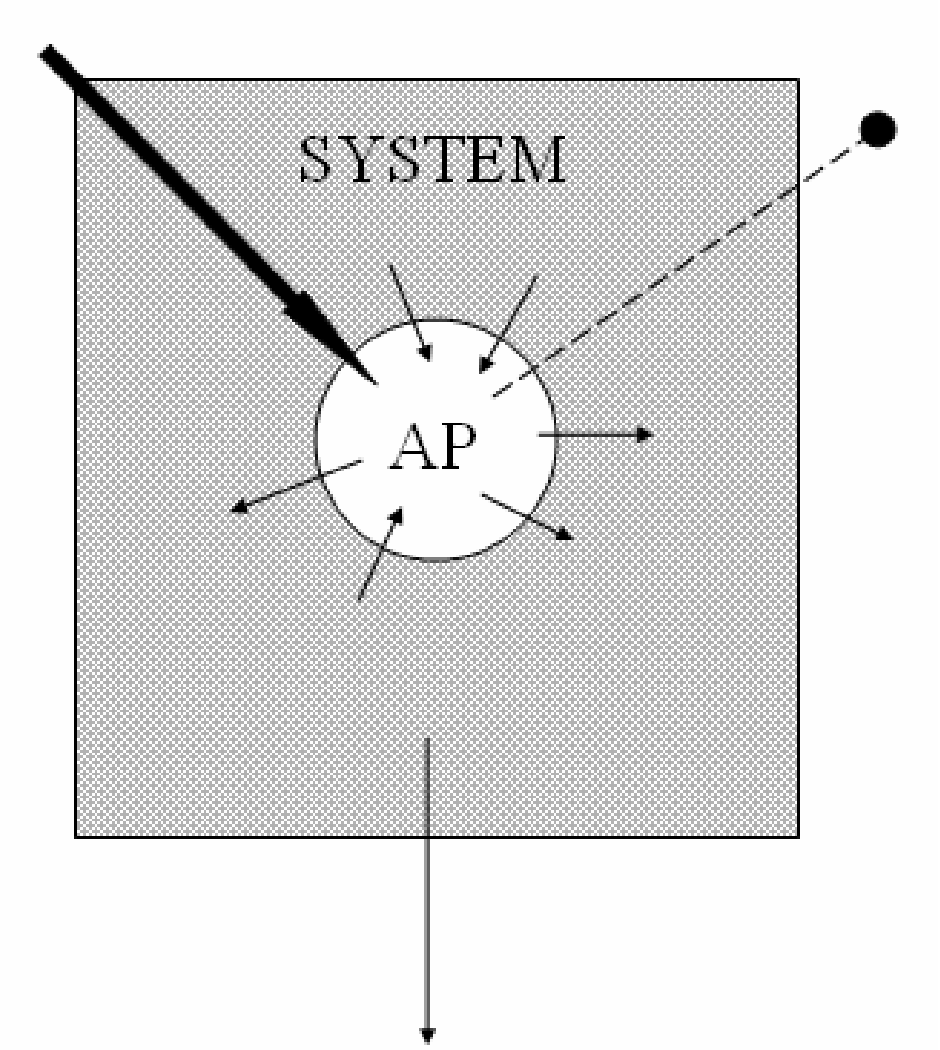
Lumped parameter models

* Models which make the system discrete through a lumping process thus eliminating the need to deal with partial differential equations.
* Classes of such models:
  - Noncompartmental models (algebraic equations)
  - Compartmental models (linear or nonlinear differential equations)

The system

* Accessible pools: These are pools that are available to the experimentalist for test input and/or measurement.
* Nonaccessible pools: These are pools comprising the rest of the system which are not available for test input and/or measurement.

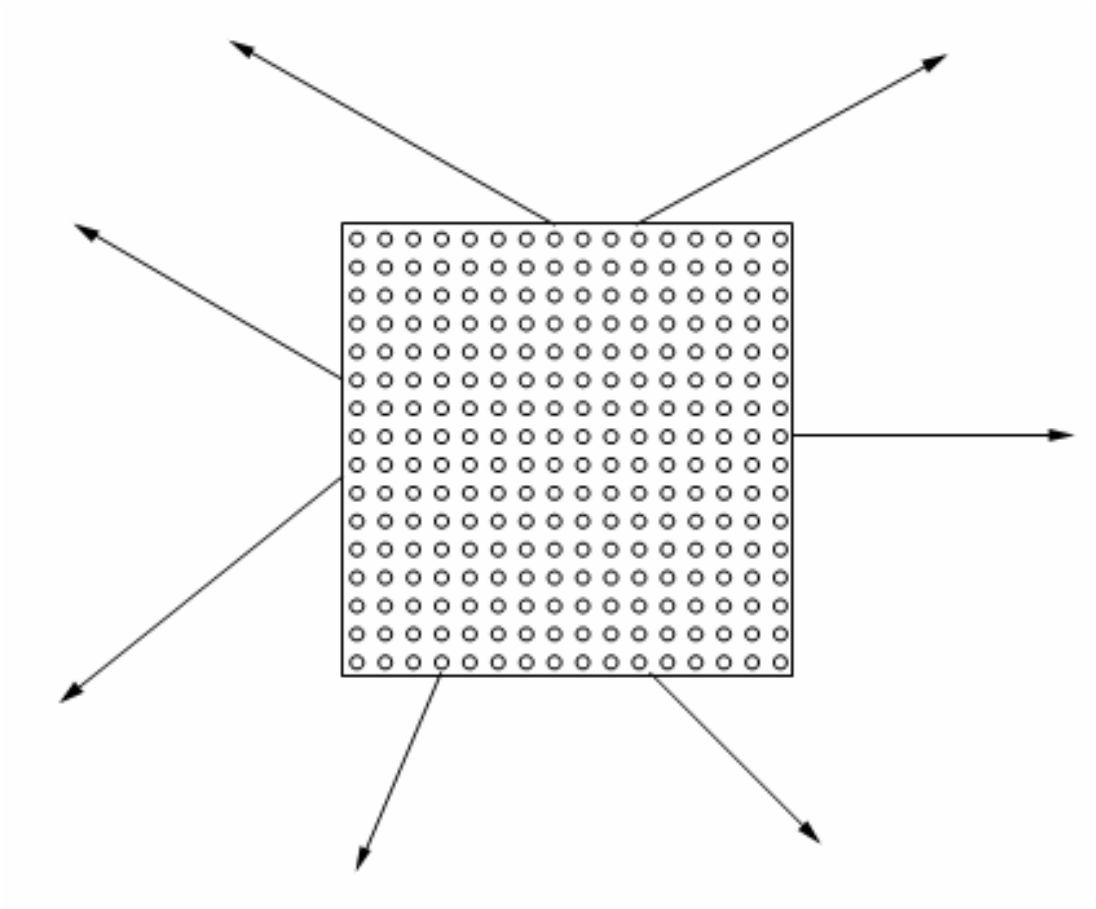
An accessible pool



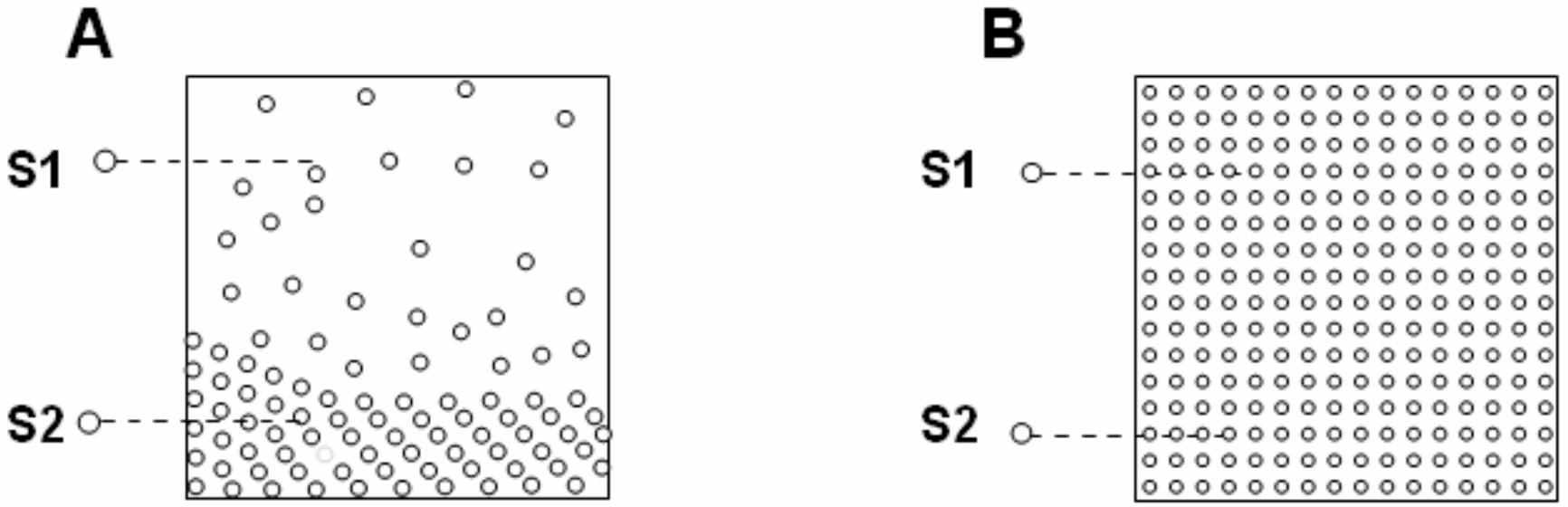
Characteristics of the accessible pool

* Kinetically homogeneous
* Instantaneous and well-mixed

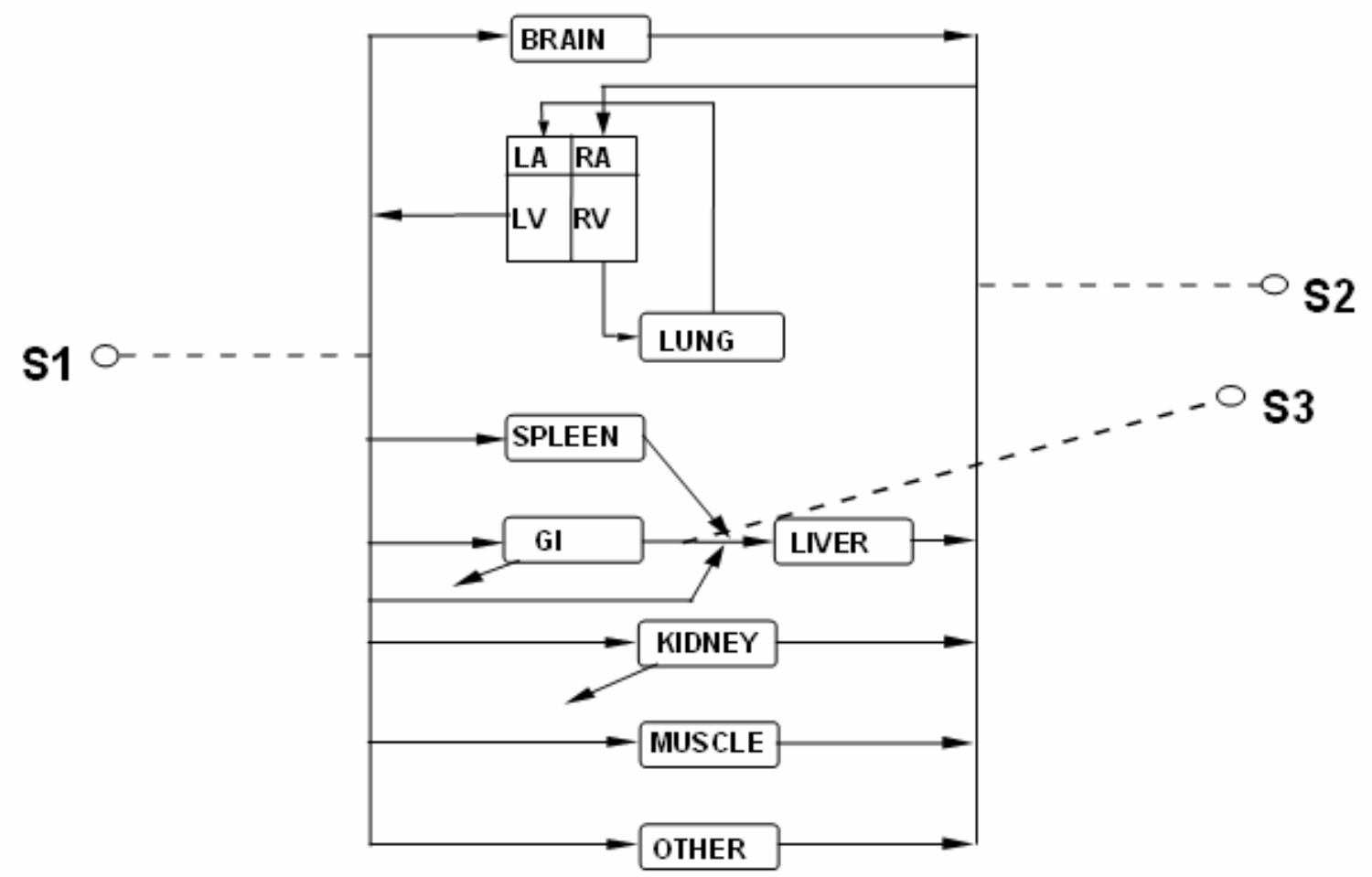
Kinetic homogeneity



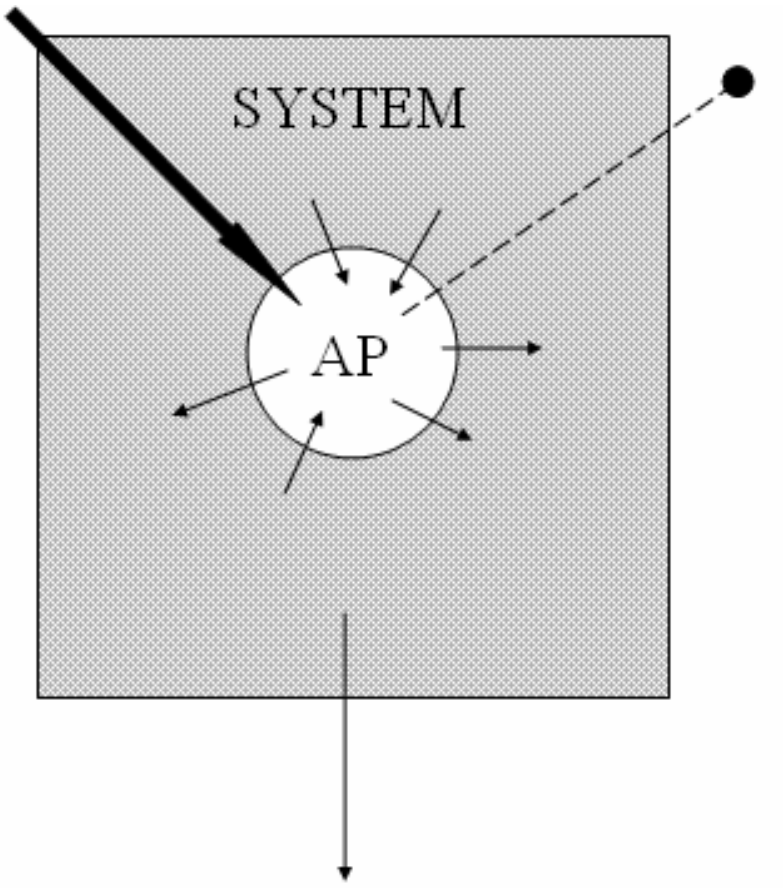
Instantaneous and well-mixed



Instantaneous and well-mixed

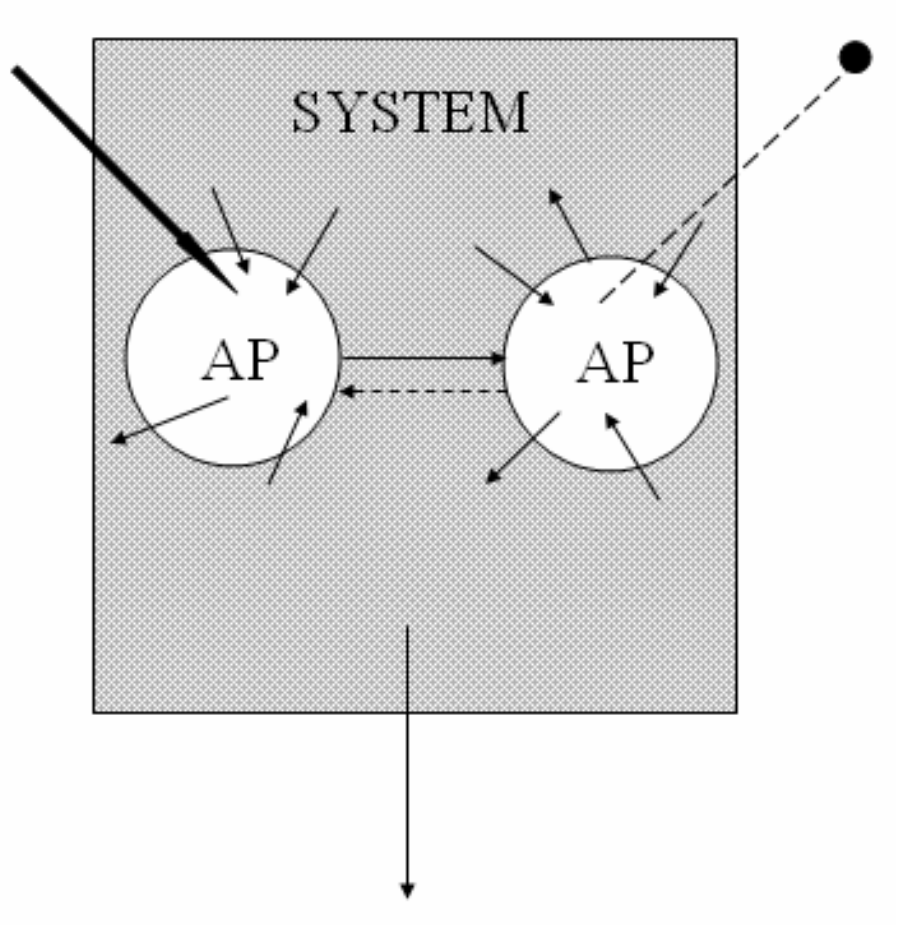


The single accessible pool



E.g. Direct input into plasma with plasma samples.

The two accessible pools



E.g. Oral dosing or plasma and urine samples.

The pharmacokinetic parameters

The pharmacokinetic parameters estimated using kinetic data characterize both the kinetics in the accessible pool, and the kinetics in the whole system.

Accessible pool parameters

* Volume of distribution
* Clearance rate
* Elimination rate constant
* Mean residence time

System parameters

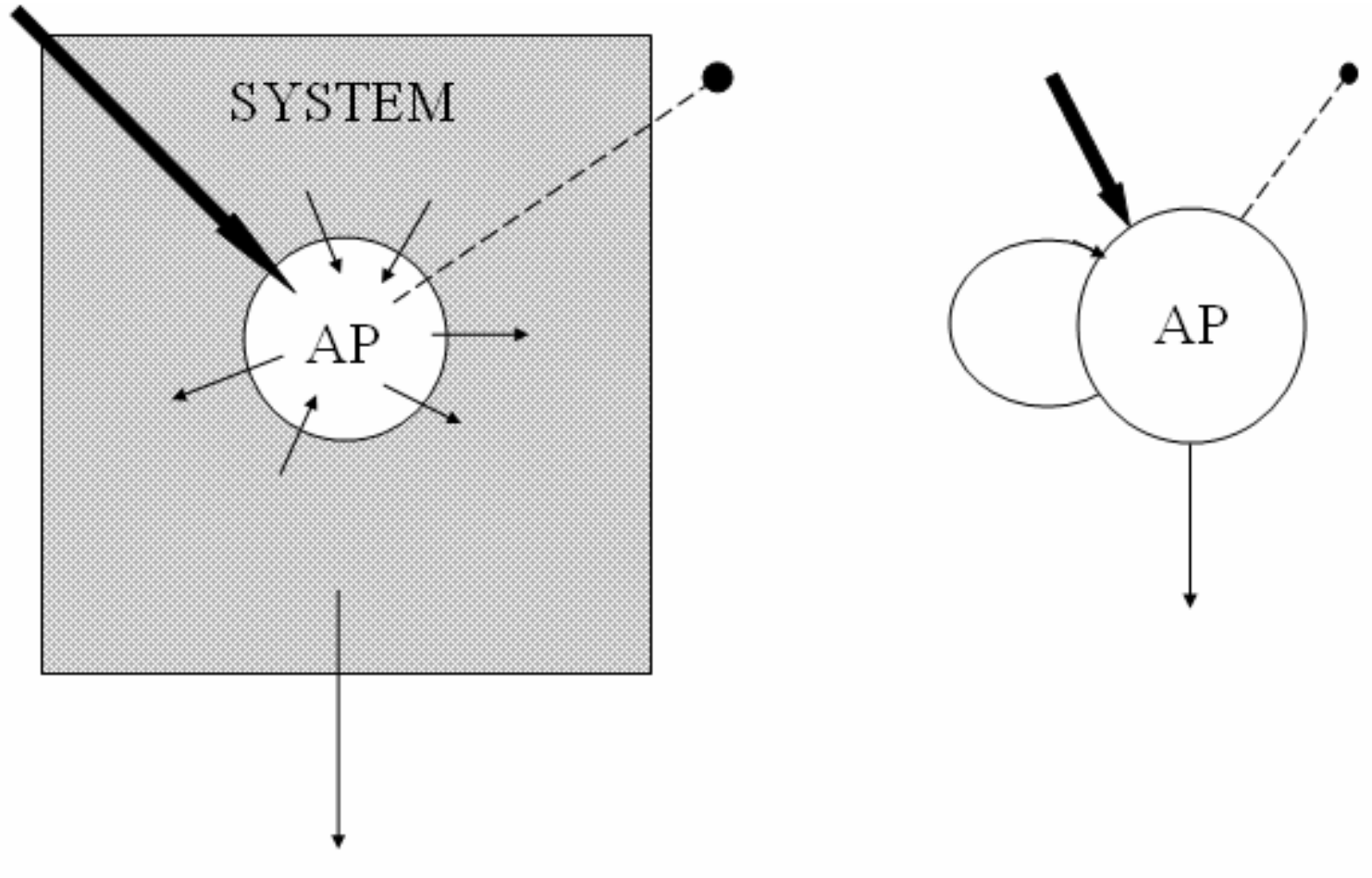
* Equivalent volume of distribution
* System mean residence time
* Bioavailability
* Absorption rate constant

Models to estimate the pharmacokinetic parameters

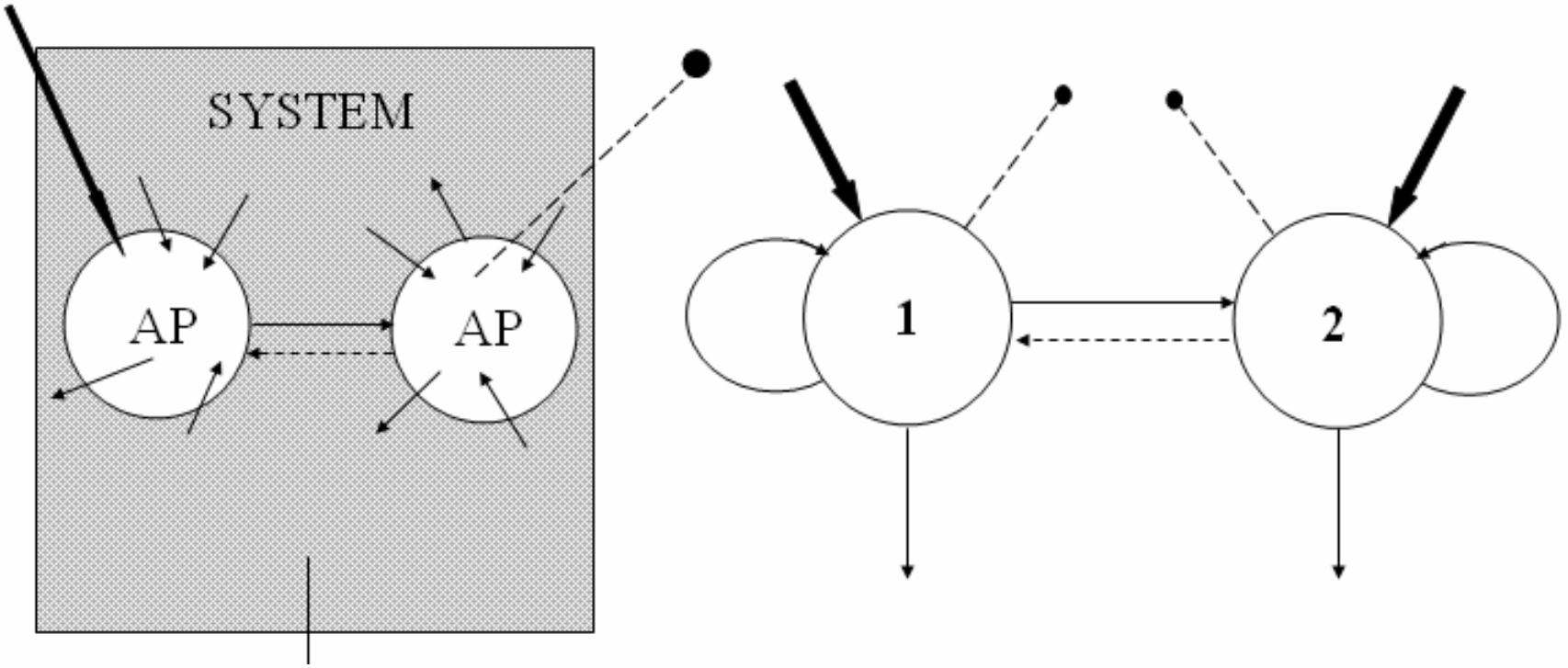
The difference between noncompartmental and compartmental models is how the nonaccessible portion of the system is described.

The noncompartmental model

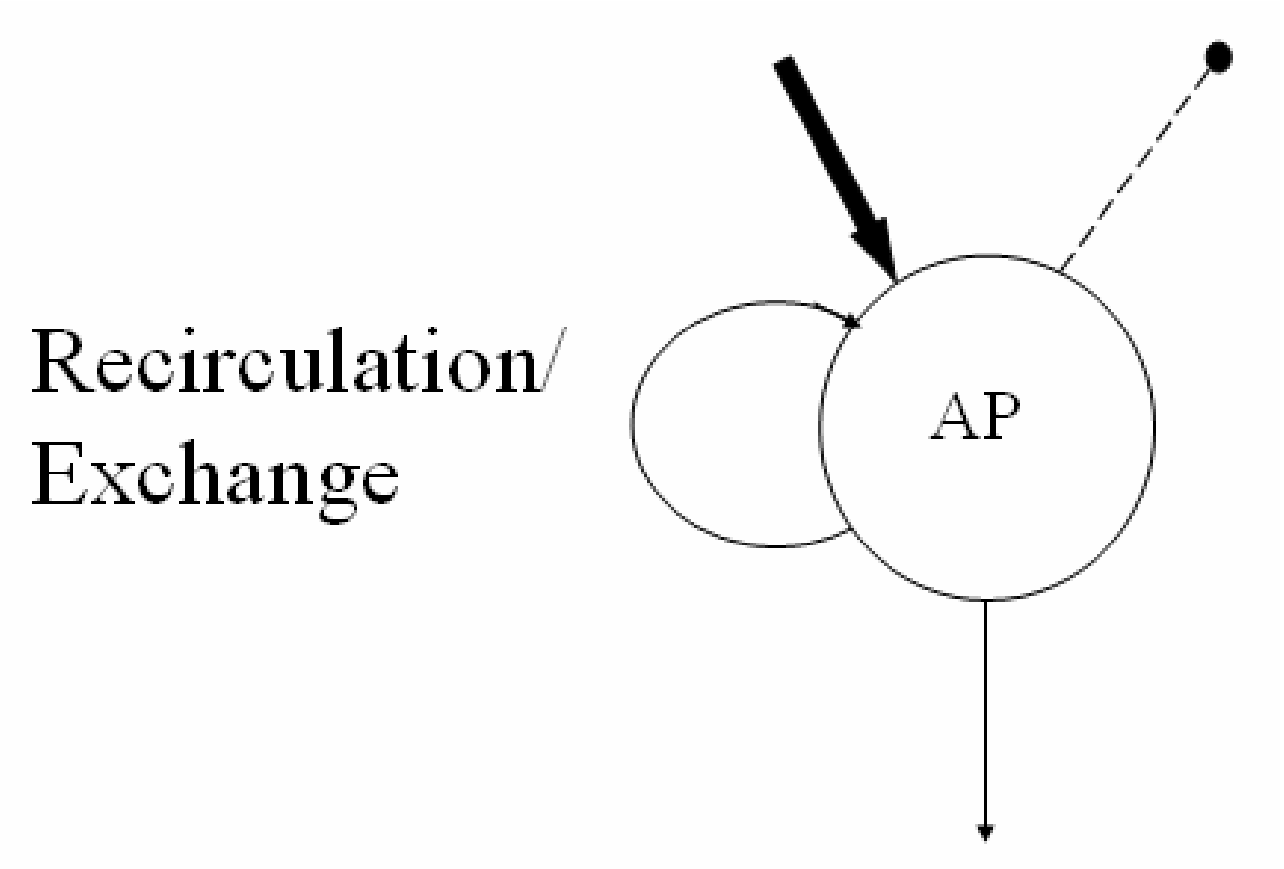
Single accessible pool model



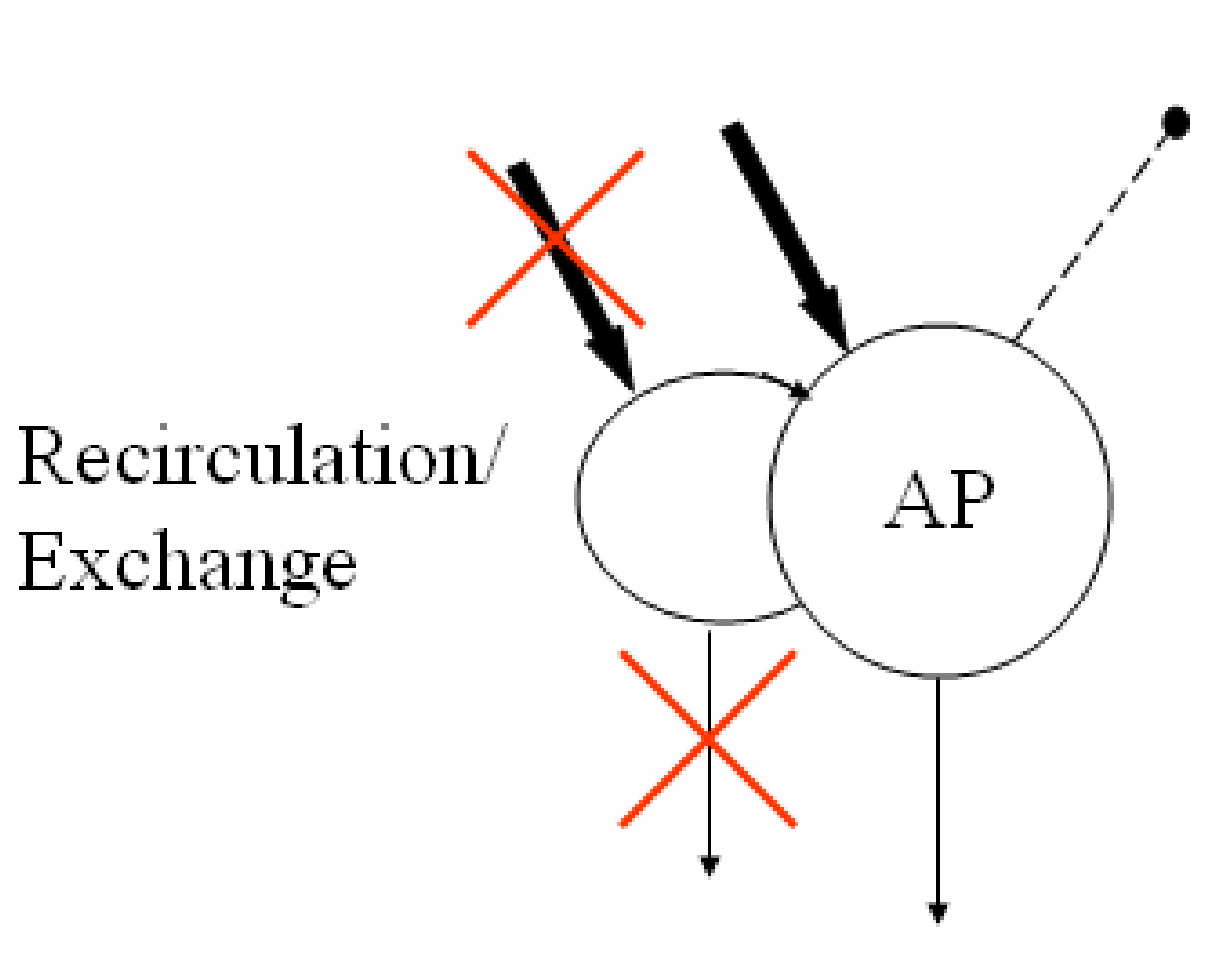
Two accessible pool model



Recirculation-exchange arrow



Recirculation-exchange arrow



Single accessible pool model

* Parameters (bolus and infusion)
* Estimating the parameters from data

Single accessible pool model parameters

Bolus	Infusion
$V_a = \frac{d}{C(0)}$	$V_a = \frac{u}{\dot{C}(0)}$
$CL_a = \frac{d}{AUC}$	$CL_a = \frac{u}{\overline{C}}$
$MRT_s = \frac{AUMC}{AUC}$	$MRT_s = \frac{\int_0^\infty [\overline{C} - C(t)]dt}{\overline{C}}$

d – dose; *u* – infusion rate; *C(t)* – concentration; *AUC* – area under curve (1st moment); *AUMC* – mean area under curve (2nd moment);
– steady state concentration.

What is needed?

* Estimates for C(0), C(0) and/or C.
* Estimates for AUC and AUMC.

All require extrapolations beyond the time frame of the experiment. Thus this method is not model independent as often claimed.

The integrals

$$AUC = \int_0^{\infty} C(t)dt = \int_0^{t_1} C(t)dt + \int_{t_1}^{t_n} C(t)dt + \int_{t_n}^{\infty} C(t)dt$$

$$AUMC = \int_0^{\infty} t \cdot C(t)dt = \int_0^{t_1} t \cdot C(t)dt + \int_{t_1}^{t_n} t \cdot C(t)dt + \int_{t_n}^{\infty} t \cdot C(t)dt$$

Estimating AUC and AUMC using sums of exponentials

Bolus

$$C(t) = A_1 e^{-\lambda_1 t} + \cdots + A_n e^{-\lambda_n t}$$

Infusion

$$C(t) = A_0 + A_1 e^{-\lambda_1 t} + \cdots + A_n e^{-\lambda_n t}$$

$$A_0 + A_1 + \cdots + A_n = 0$$

Bolus Injection

$$AUC = \int_0^\infty C(t)dt = \frac{A_1}{\lambda_1} + \cdots + \frac{A_n}{\lambda_n}$$

$$AUMC = \int_0^\infty t \cdot C(t)dt = \frac{A_1}{\lambda_1^2} + \cdots + \frac{A_n}{\lambda_n^2}$$

And in addition:

$$C(0) = A_1 + \cdots + A_n$$

Infusion

$$\int_0^\infty [\overline{C} - C(t)]dt = \frac{A_1}{\lambda_1} + \cdots + \frac{A_n}{\lambda_n}$$

And in addition:

$$\dot{C}(0) = -A_1\lambda_1 - \cdots - A_n\lambda_n$$

Estimating AUC and AUMC using other methods

* Trapezoidal
* Log-trapezoidal
* Combinations
* Other
* Extrapolating

The Integrals

$$AUC = \int_0^{\infty} C(t)dt = \int_0^{t_1} C(t)dt + \int_{t_1}^{t_n} C(t)dt + \int_{t_n}^{\infty} C(t)dt$$

$$AUMC = \int_0^{\infty} t \cdot C(t)dt = \int_0^{t_1} t \cdot C(t)dt + \int_{t_1}^{t_n} t \cdot C(t)dt + \int_{t_n}^{\infty} t \cdot C(t)dt$$

The other methods provide formulas for the integrals between t_1 and t_n leaving it up to the researcher to extrapolate to time zero and time infinity.

Trapezoidal rule

$$AUC_{i-1}^{i} = \frac{1}{2}(y_{obs}(t_i) + y_{obs}(t_{i-1})(t_i - t_{i-1})$$

$$AUMC_{i-1}^{i} = \frac{1}{2}(t_i \cdot y_{obs}(t_i) + t_{i-1} \cdot y_{obs}(t_{i-1})(t_i - t_{i-1})$$

Log-trapezoidal rule

$$AUC_{i-1}^{i} = \frac{1}{\ln\left(\frac{y_{obs}(t_i)}{y_{obs}(t_{i-1})}\right)}(y_{obs}(t_i) + y_{obs}(t_{i-1})(t_i - t_{i-1})$$

$$AUMC_{i-1}^{i} = \frac{1}{\ln\left(\frac{y_{obs}(t_i)}{y_{obs}(t_{i-1})}\right)}(t_i \cdot y_{obs}(t_i) + t_{i-1} \cdot y_{obs}(t_{i-1})(t_i - t_{i-1})$$

Extrapolating from t_n to infinity

* Terminal decay is a monoexponential often called λ_z.

* Half-life of terminal decay calculated:

$$t_{z/1/2} = \ln(2)/ \lambda_z$$

Extrapolating from t_n to infinity

From last datum:

$$AUC_{extrap-dat} = \int_{t_n}^{\infty} C(t)dt = \frac{y_{obs}(t_n)}{\lambda_z}$$

$$AUMC_{extrap-dat} = \int_{t_n}^{\infty} t \cdot C(t)dt = \frac{t_n \cdot y_{obs}(t_n)}{\lambda_z} + \frac{y_{obs}(t_n)}{\lambda_z^2}$$

From last calculated value:

$$AUC_{extrap-calc} = \int_{t_n}^{\infty} C(t)dt = \frac{A_z e^{-\lambda_z t_n}}{\lambda_z}$$

$$AUMC_{extrap-calc} = \int_{t_n}^{\infty} t \cdot C(t)dt = \frac{t_n \cdot A_z e^{-\lambda_z t_n}}{\lambda_z} + \frac{A_z e^{-\lambda_z t_n}}{\lambda_z^2}$$

Estimating the Integrals

To estimate the integrals, one sums up the individual components.

$$AUC = \int_0^{\infty} C(t)dt = \int_0^{t_1} C(t)dt + \int_{t_1}^{t_n} C(t)dt + \int_{t_n}^{\infty} C(t)dt$$

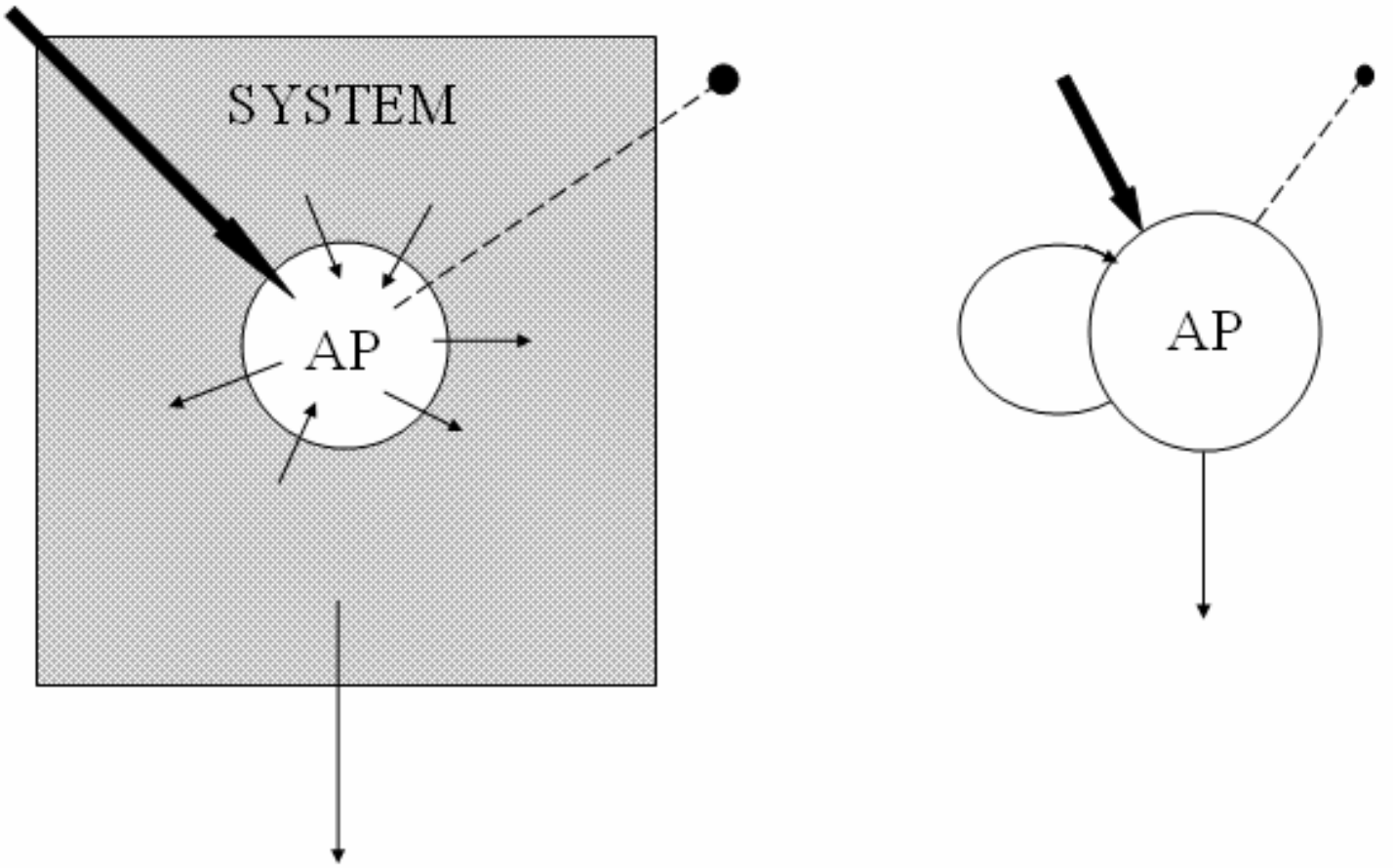
$$AUMC = \int_0^{\infty} t \cdot C(t)dt = \int_0^{t_1} t \cdot C(t)dt + \int_{t_1}^{t_n} t \cdot C(t)dt + \int_{t_n}^{\infty} t \cdot C(t)dt$$

Advantages of using sums of exponentials

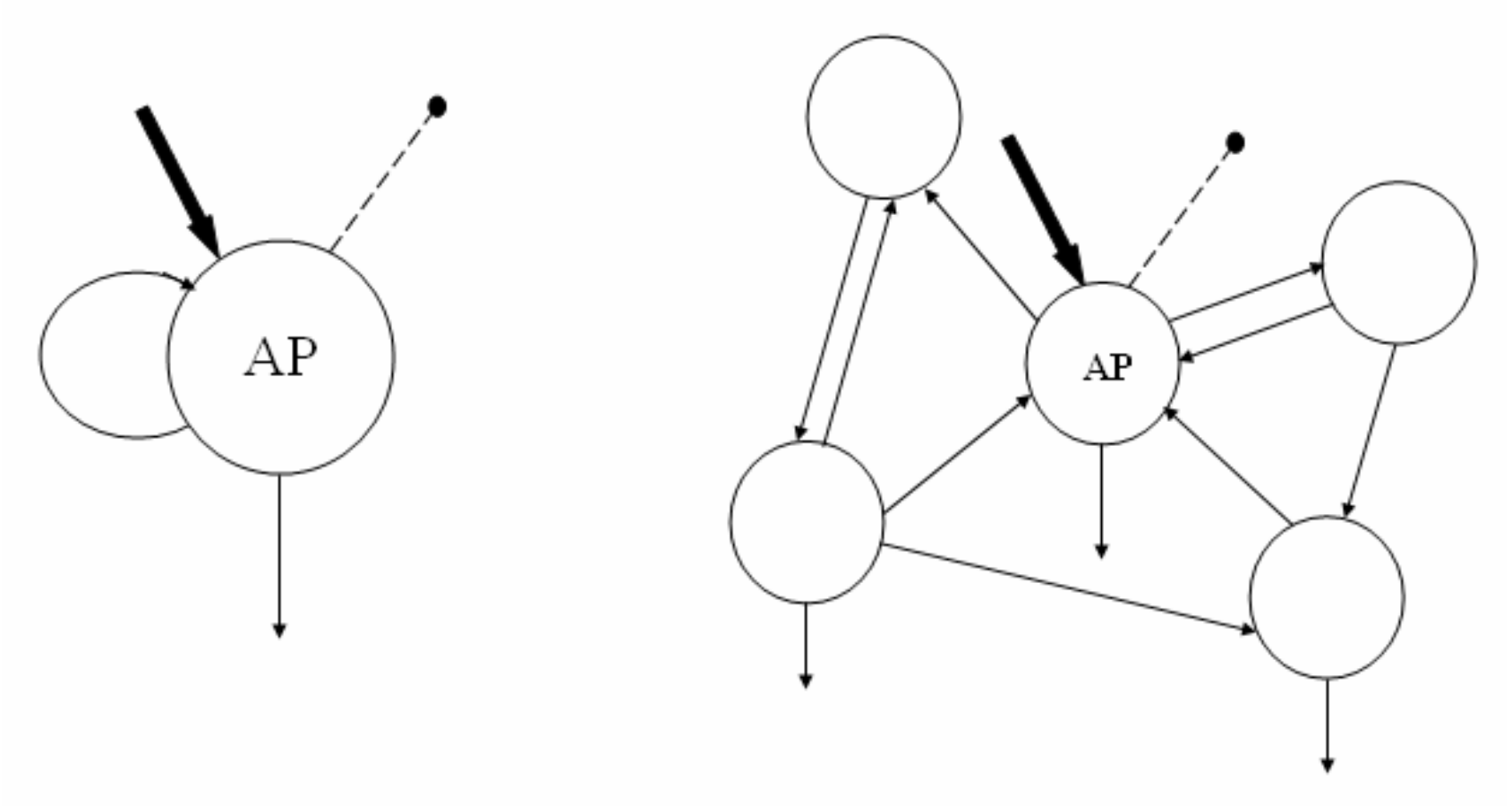
* Extrapolation done as part of the data fitting
* Statistical information of all parameters calculated
* Natural connection with the solution of linear, constant coefficient compartmental models
* Software easily available

The Compartmental Model

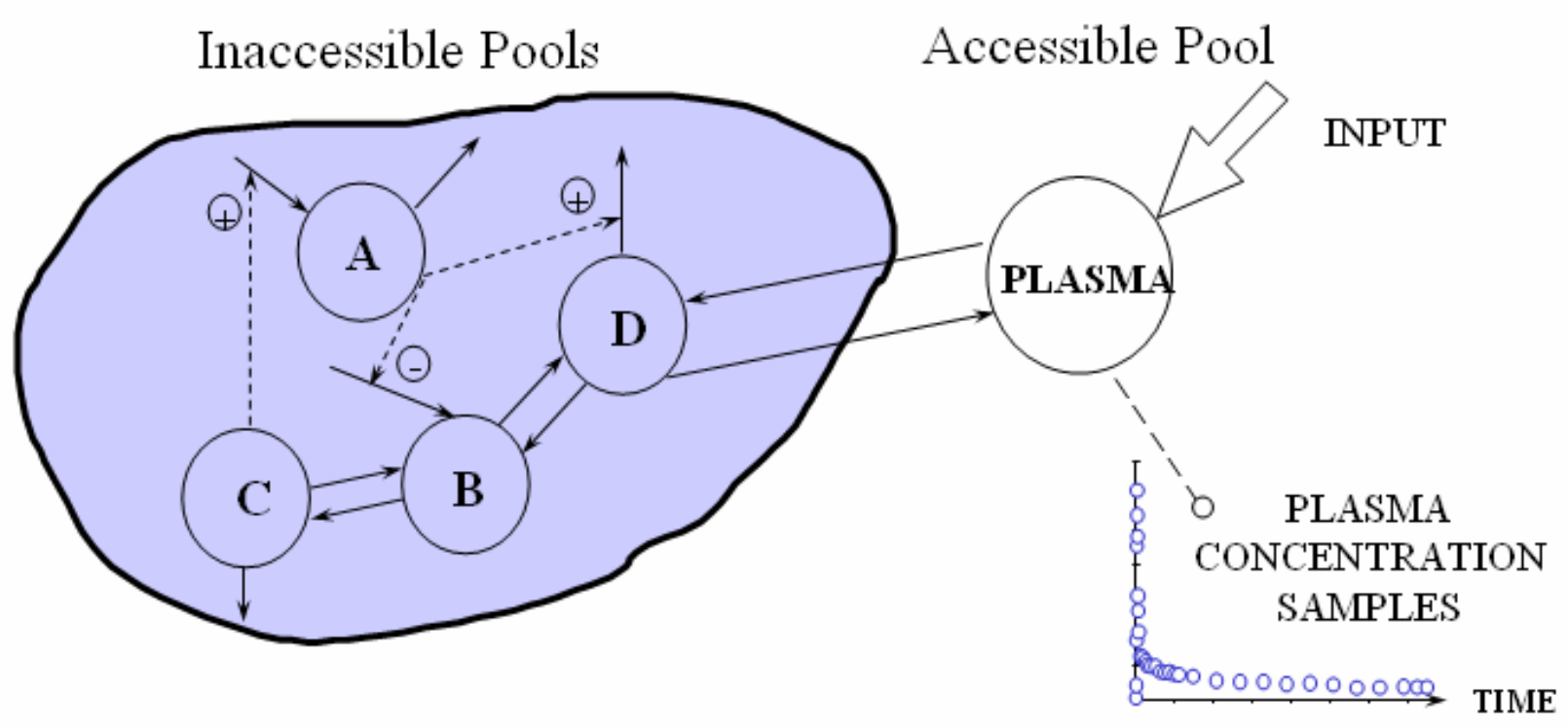
Single Accessible Pool



Single Accessible Pool

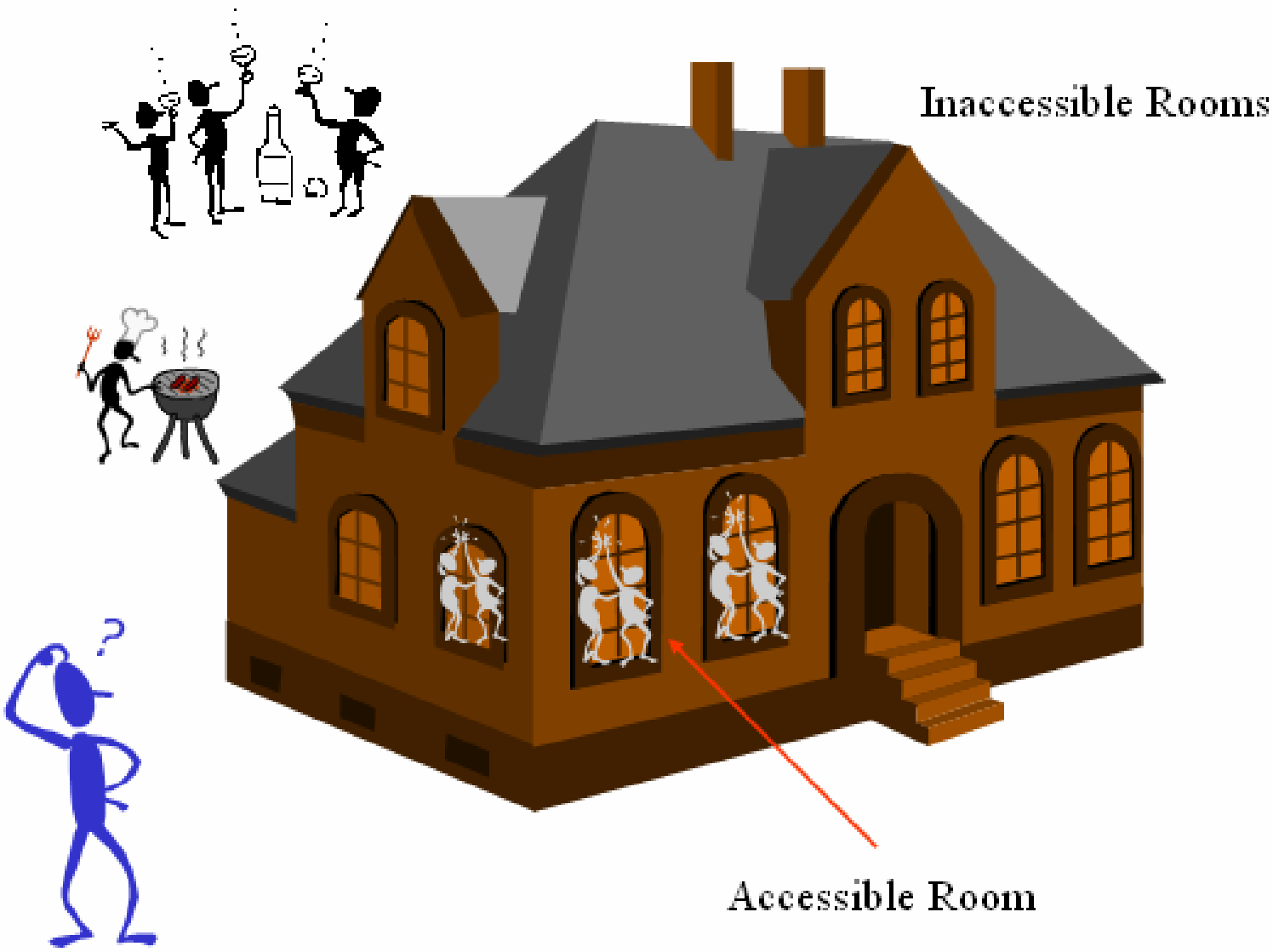


A model of the system



Key Concept: Predicting inaccessible features of the system based upon measurements in the accessible pool, while estimating specific parameters of interest.

A model of the system



Compartmental model

* Compartment
  - instantaneously well-mixed
  - kinetically homogeneous
* Compartmental model
  - finite number of compartments
  - specifically connected
  - specific input and output

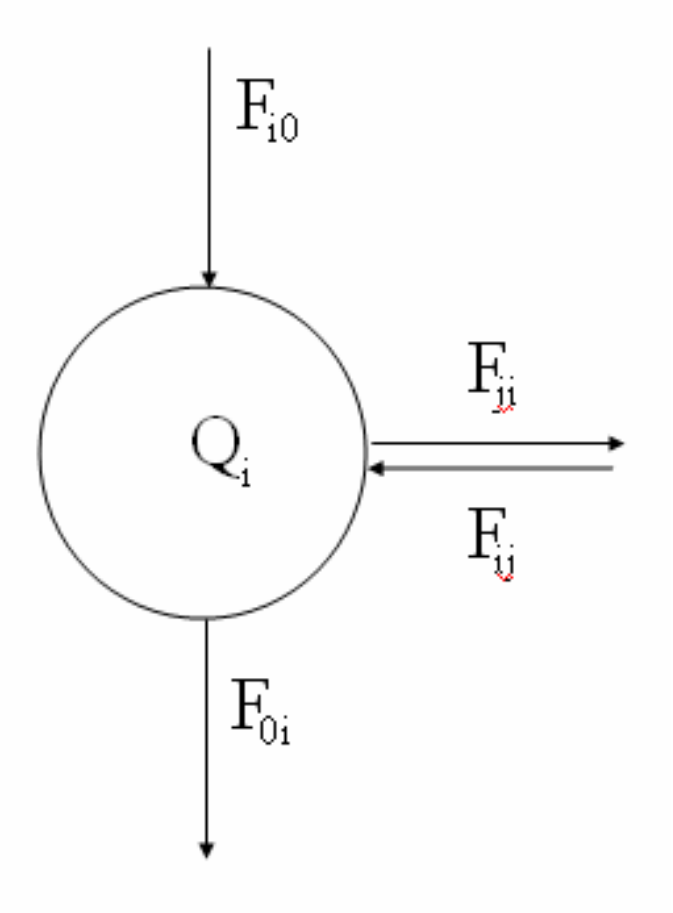
Kinetics and the compartmental model

Time and Space $\quad \frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}, \frac{\partial}{\partial t} \quad X(x, y, z, t)$

Time $\quad \frac{d}{dt} \quad X(t) \quad \frac{dX}{dt}$

Abducted by an alien circus company, Professor Doyle is forced to write calculus equations in center ring.

Notation



F_{ij} are transport in units mass/time.

The F_{ij}

* Describe movement among, into or out of a compartment
* A composite of metabolic activity
  - transport
  - biochemical transformation
  - both
* Similar time frame

The F_{ij}

$$F_{ji}(\vec{Q}, \vec{p}, t) = k_{ji}(\vec{Q}, \vec{p}, t) \cdot Q_i(t)$$

(ref: see Jacquez and Simon)

The k_{ij}

The k_{ij} are called fractional transfer functions.

If the following is constant, the kij is called a fractional transfer or rate constant:

$$k_{ij}(\vec{Q}, \vec{p}, t) = k_{ij}$$

Compartmental models and systems of ordinary differential equations

* Well mixed: permits writing $Q_i(t)$ for the i^{th} compartment.
* Kinetic homogeneity: permits connecting compartments via the k_{ij}.

The ith compartment

$$\frac{dQ_i}{dt} = -\left(\sum_{\substack{j=0 \\ j\neq i}}^{n} k_{ji}(\vec{Q}, \vec{p}, t)\right) Q_i(t) + \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}(\vec{Q}, \vec{p}, t) Q_j(t) + F_{i0}$$

Rate of change of Q_i

Fractional loss of Q_i

Fractional input from Q_j

Input from "outside"

Linear, constant coefficient compartmental models

* All transfer rates k_{ij} are constant.
* Assumes “steady state” conditions.

The i^{th} compartment

$$\frac{dQ_i}{dt} = -\left(\sum_{\substack{j=0 \\ j\neq i}}^{n} k_{ji}\right) Q_i(t) + \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}\, Q_j(t) + F_{i0}$$

The compartmental matrix

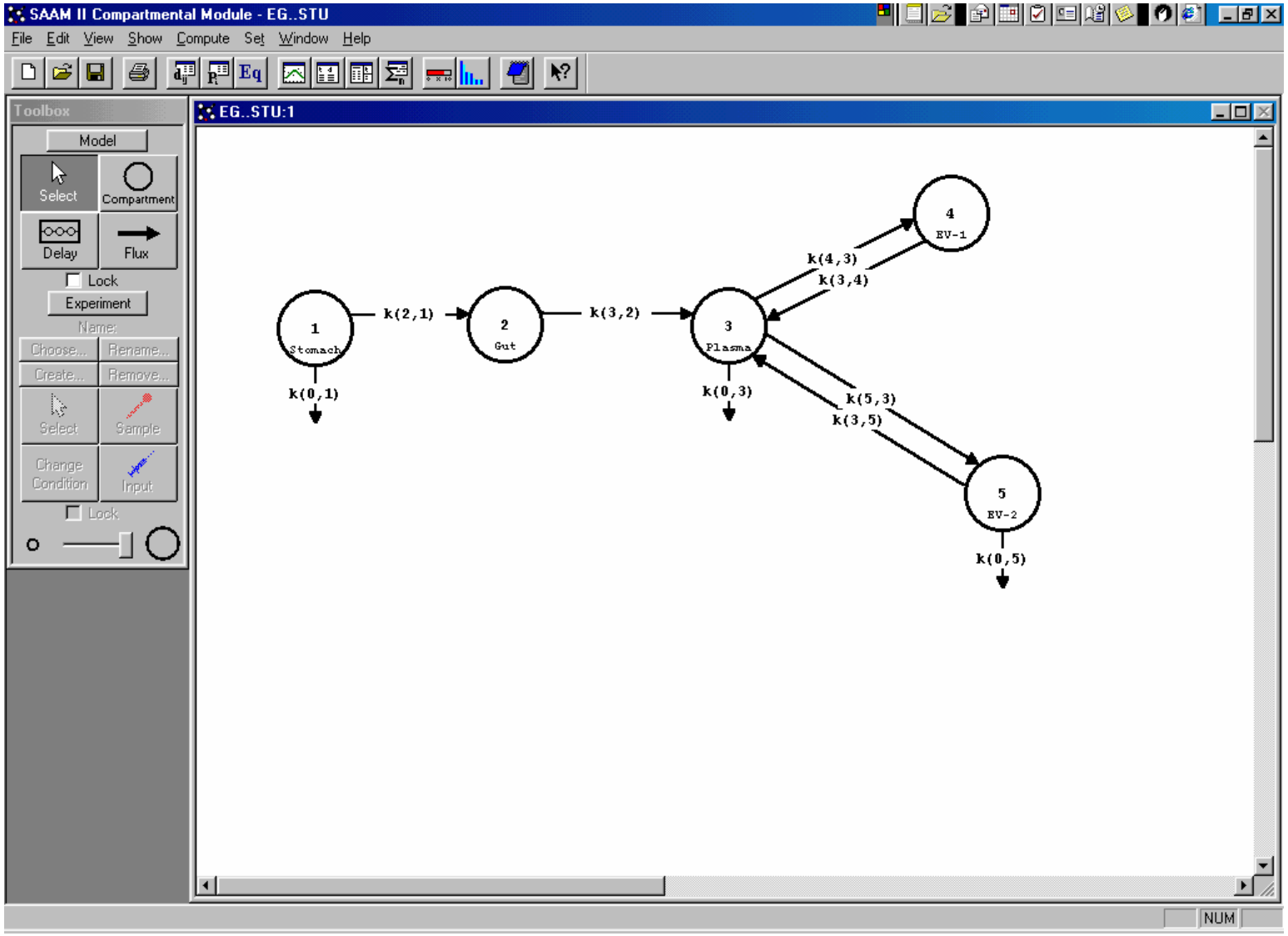
$$k_{ii} = -\left(\sum_{\substack{j=0 \\ j \neq i}}^{n} k_{ji} \right)$$

$$K = \begin{bmatrix} k_{11} & k_{12} & \cdots & k_{1n} \\ k_{21} & k_{22} & \cdots & k_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ k_{n1} & k_{n2} & \cdots & k_{nn} \end{bmatrix}$$

Compartmental model

* A postulation of how one believes a system functions.
* The need to perform the same experiment on the model as one did in the laboratory.

Example using SAAM II



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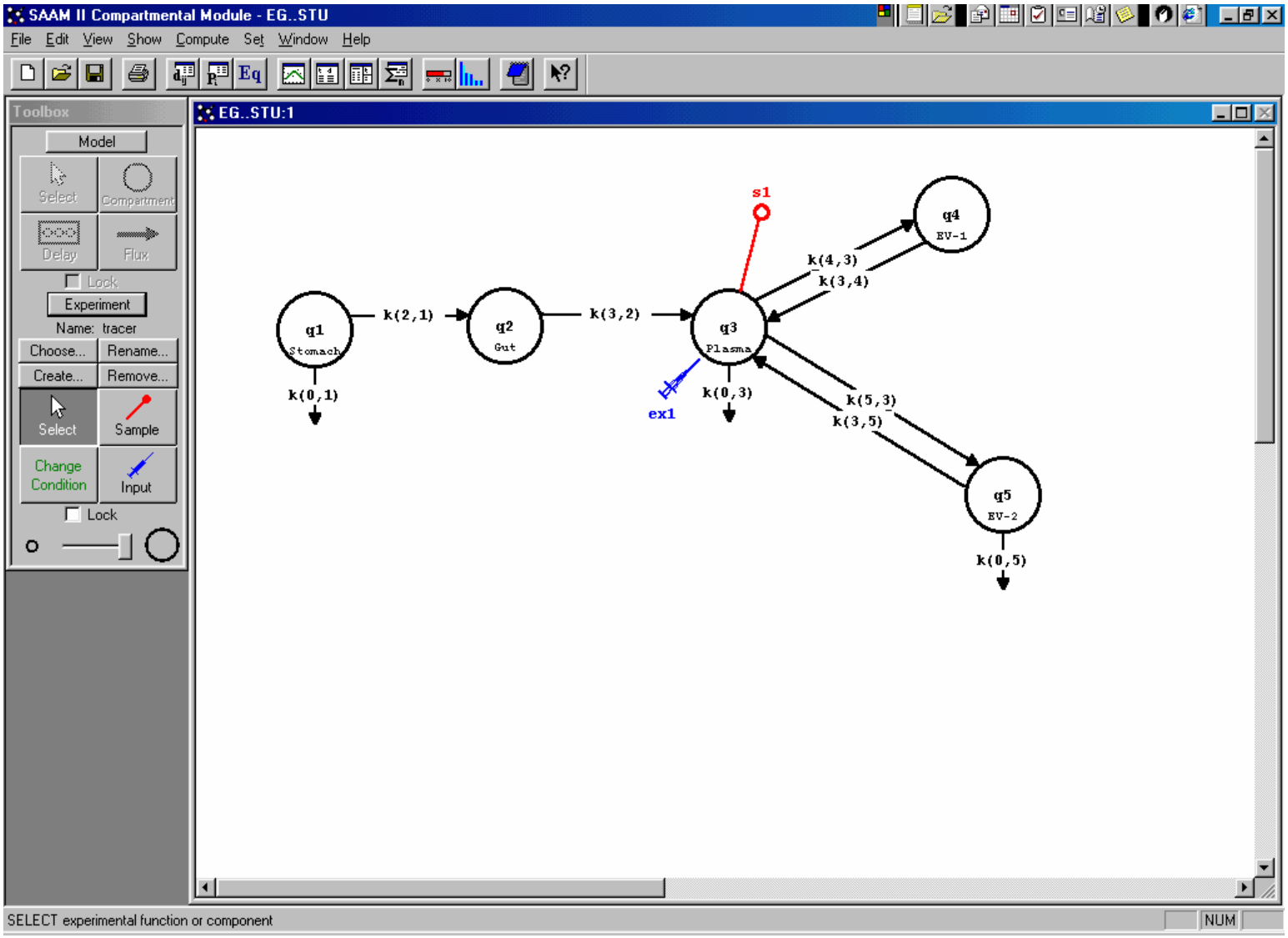
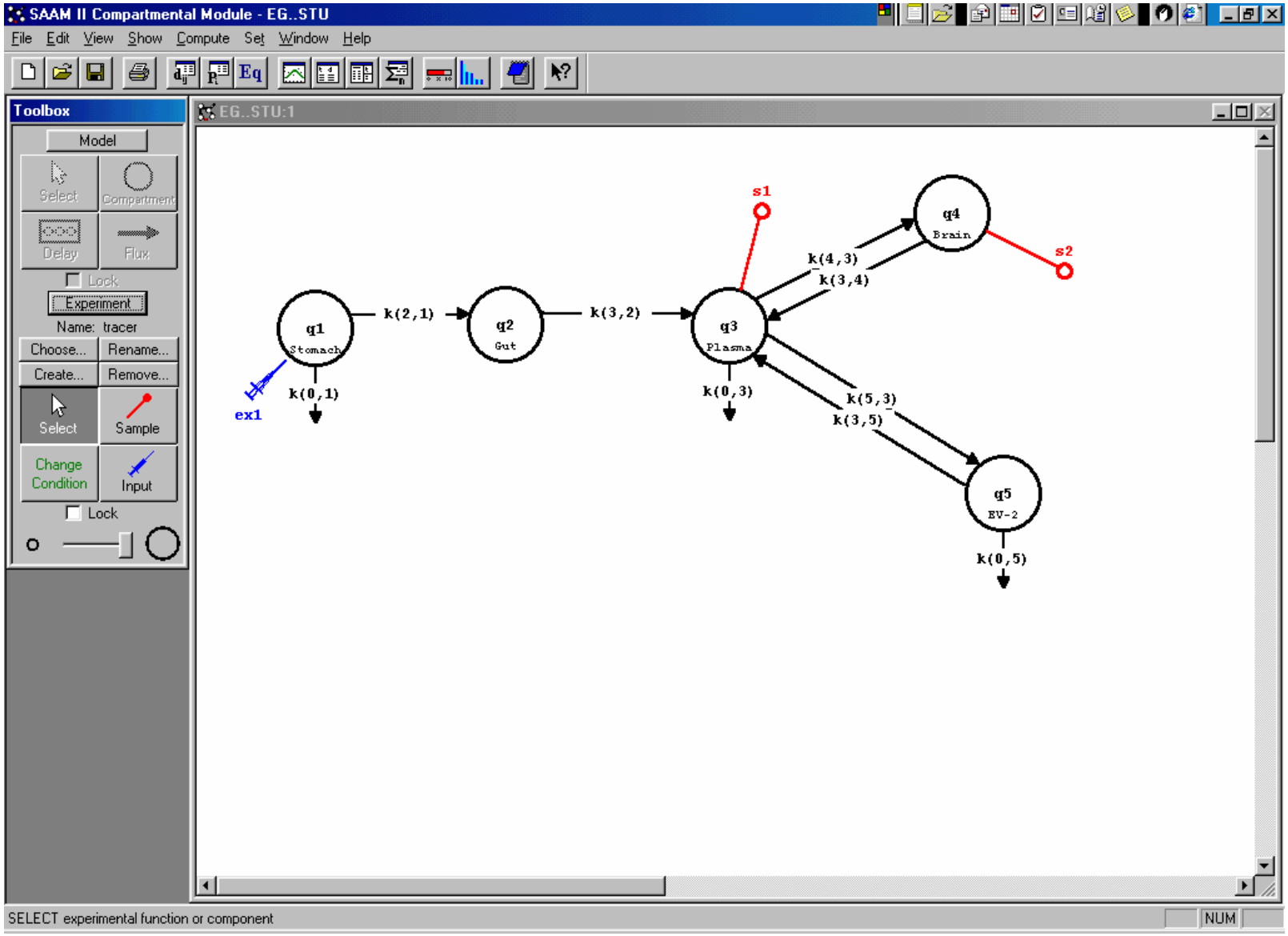


Example using SAAM II

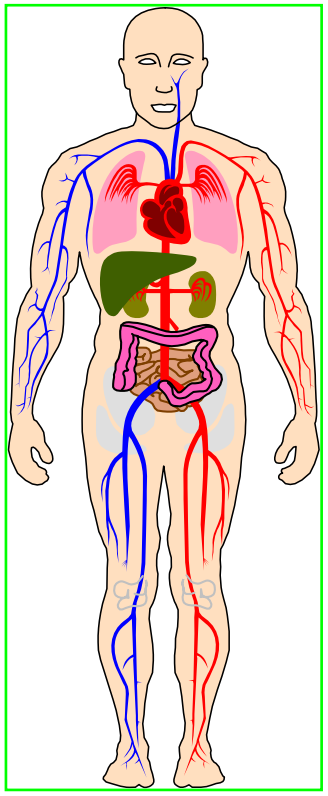


Experiments

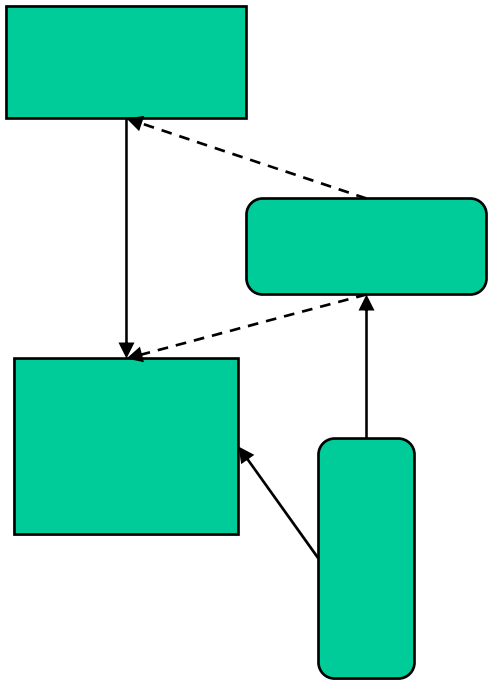
* Need to recreate the laboratory experiment on the model.
* Need to specify input and measurements
* Key: UNITS

Model of the System?

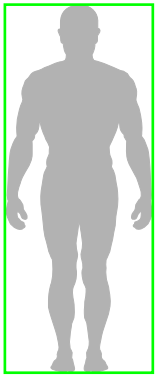
Reality (Data)



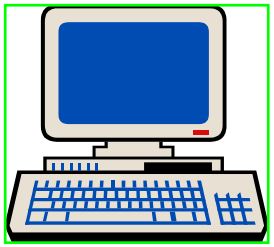
Conceptualization (Model)



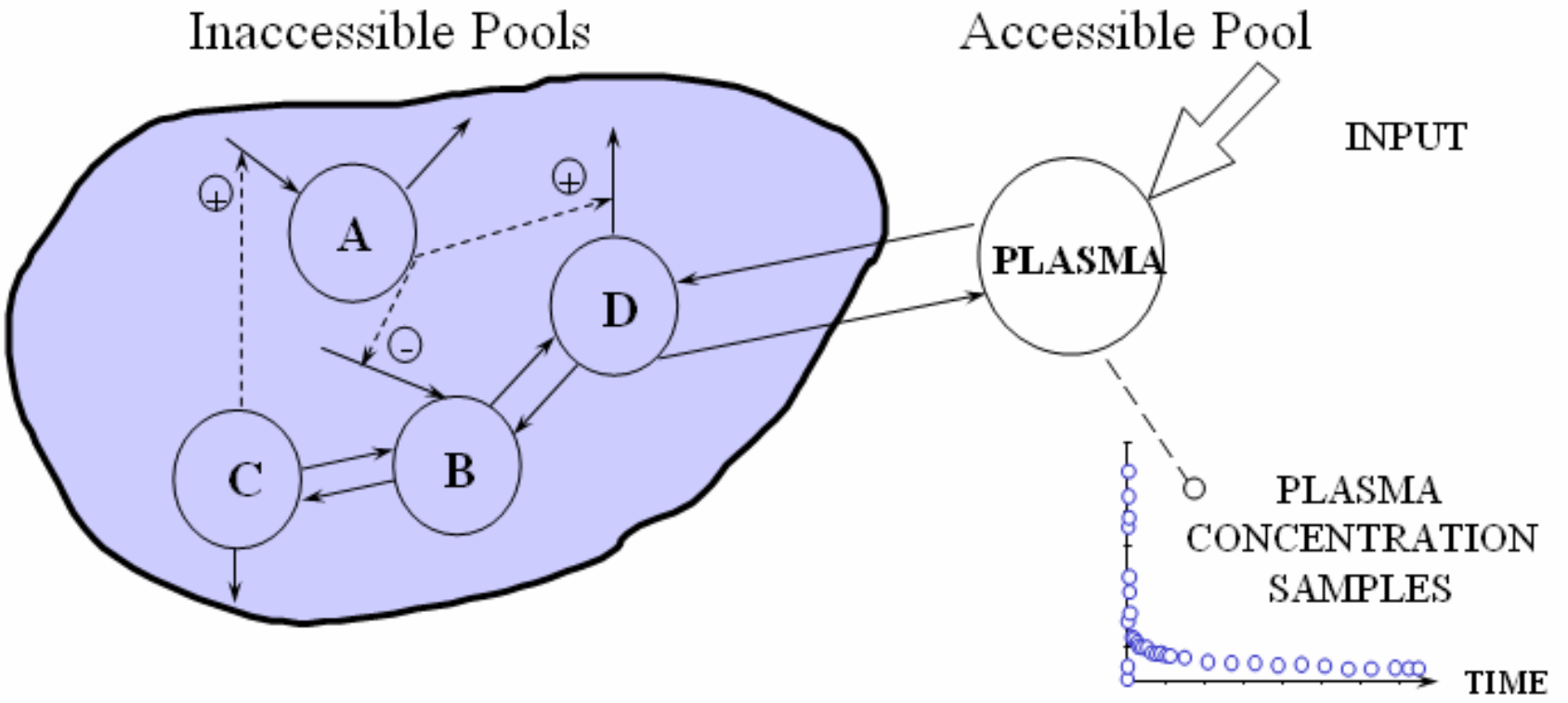
Data Analysis and Simulation



```
program optimize
    begin model
    …
    end
```

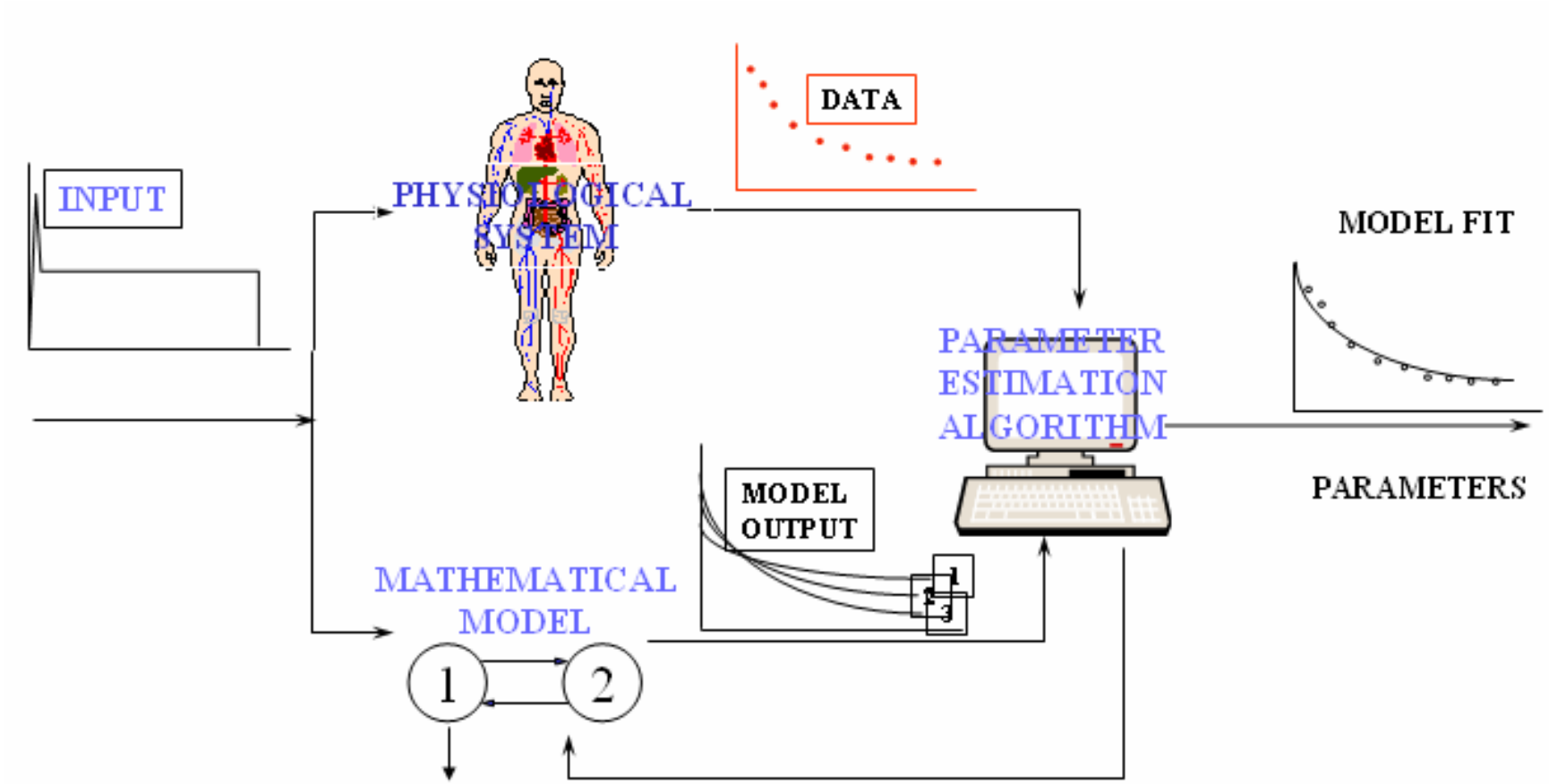


A Model of the System



Key Concept: Predicting inaccessible features of the system based upon measurements in the accessible pool, while estimating specific parameters of interest.

Parameter Estimation



Parameter estimates

* Model parameters: k_{ij} and volumes
* Pharmacokinetic parameters: volumes, clearance, residence times, etc.
* Reparameterization - changing the paramters from k_{ij} to the PK parameters.

Recovering the PK parameters from the compartmental model

* Parameters based upon the model primary parameters
* Parameters based upon the compartmental matrix

Parameters based upon the model primary parameters

* Functions of model primary parameters

* Clearance = volume * $k_{(0,1)}$

Parameters based upon the compartmental matrix

$$K = \begin{bmatrix} k_{11} & k_{12} & \cdots & k_{1n} \\ k_{21} & k_{22} & \cdots & k_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ k_{n1} & k_{n2} & \cdots & k_{nn} \end{bmatrix} \qquad \Theta = -K^{-1} = \begin{pmatrix} \vartheta_{11} & \vartheta_{12} & \cdots & \vartheta_{1n} \\ \vartheta_{21} & \vartheta_{22} & \cdots & \vartheta_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \vartheta_{n1} & \vartheta_{n2} & \cdots & \vartheta_{nn} \end{pmatrix}$$

Theta, the negative of the inverse of the compartmental matrix, is called the **mean residence time matrix**.

Parameters based upon the compartmental matrix

ϑ_{ij} The average time the drug entering compartment j for the first time spends in compartment i before leaving the system.

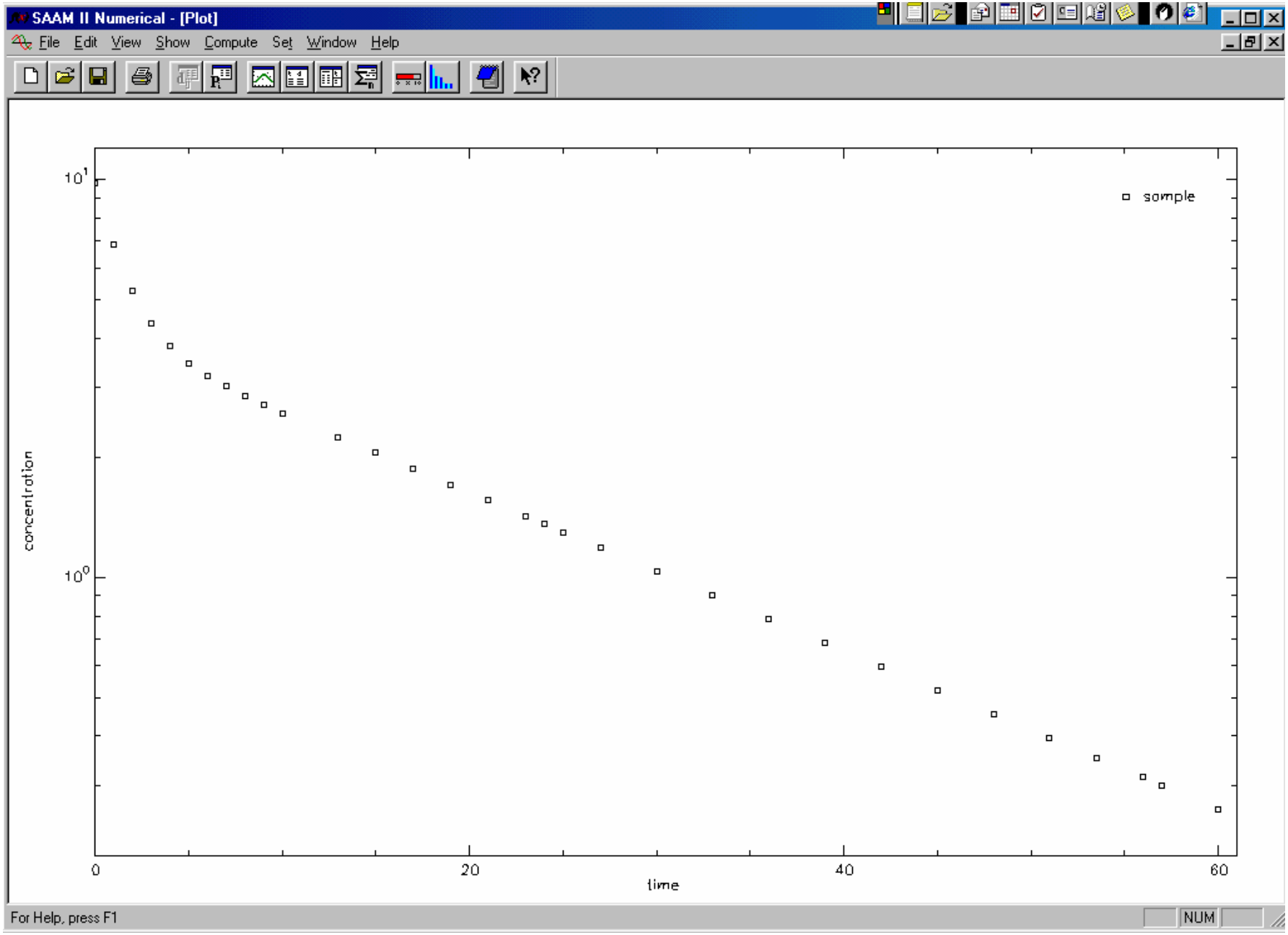
$\frac{\vartheta_{ij}}{\vartheta_{ii}}, \quad i \neq j$ The probability that a drug particle in compartment j will eventually pass through compartment i before leaving the system.

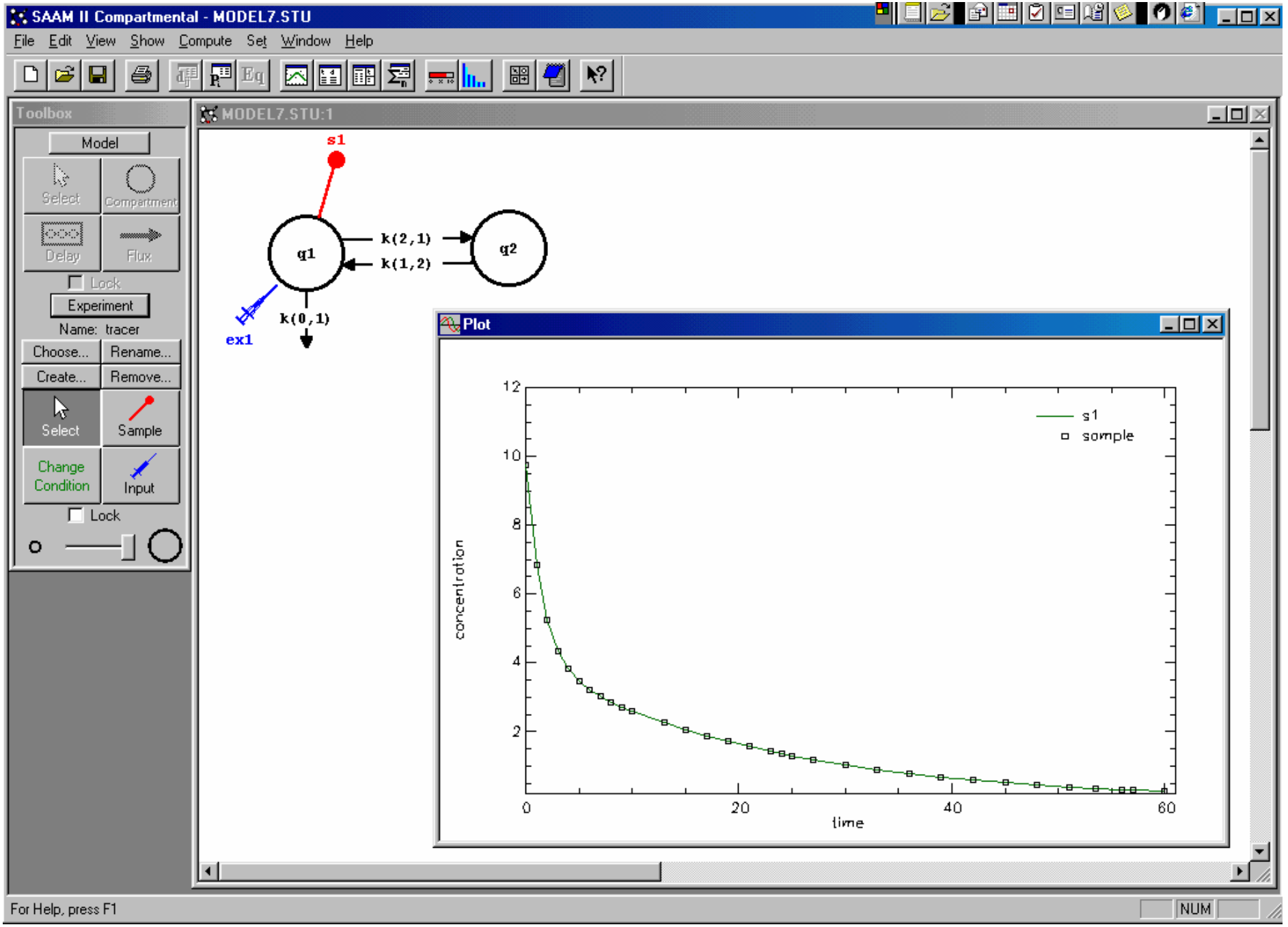
Compartmental models: advantages

* Can handle non-linearities
* Provide hypotheses about system structure
* Can aid in experimental design
* Can be used to estimate dosing regimens for Phase 1 trials

Noncompartmental versus Compartmental Approaches to PK Analysis: A Example

* Bolus injection of 100 mg of a drug into plasma. Serial plasma samples taken for 60 hours.
* Analysis using:
  - WinNonlin (“trapezoidal” integration)
  - Sums of exponentials
  - Linear compartmental model


SAAM II Numerical - [Plot]
File Edit View Show Compute Set Window Help
sample
concentration
time
10^1
10^0
0
20
40
60
For Help, press F1
NUM


SAAM II Compartmental - MODEL7.STU
File Edit View Show Compute Set Window Help
Toolbox
Model
Select
Compartment
Delay
Flux
Lock
Experiment
Name: tracer
Choose...
Rename...
Create...
Remove...
Select
Sample
Change Condition
Input
Lock
MODEL7.STU:1
s1
q1
q2
k(2,1)
k(1,2)
k(0,1)
ex1
Plot
s1
sample
concentration
time
0
20
40
60
2
4
6
8
10
12
For Help, press F1
NUM

Results

	WinNonlin	Sum of Exponentials	Compartmental Model
Volume		10.2 (9%)	10.2 (3%)
Clearance	1.02	1.02 (2%)	1.02 (1%)
MRT	19.5	20.1 (2%)	20.1 (1%)
λ_z	0.0504	.0458 (3%)	.0458 (1%)
AUC	97.8	97.9 (2%)	97.9 (1%)
AUMC	1908	1964 (3%)	1964 (1%)

Take Home Message

* To estimate the traditional pharmacokinetic parameters, either model is probably okay.
* Noncompartmental models cannot help in prediction
* Best strategy is probably a blend of compartmental to understand “system” and noncompartmental for FDA filings.

Some References

* JJ DiStefano III. Noncompartmental vs compartmental analysis: some bases for choice. Am J. Physiol. 1982;243:R1-R6
* DG Covell et. al. Mean Residence Time. Math. Biosci. 1984;72:213-2444
* Jacquez, JA and SP Simon. Qualitative theory of compartmental analysis. SIAM Review 1993;35:43-79
* Jacquez, JA. Compartmental Analysis in Biology and Medicine. BioMedware 1996. Ann Arbor, MI.
* Cobelli, C, D Foster and G Toffolo. Tracer Kinetics in Biomedical Research. Kluwer Academic/Plenum Publishers. 2000, New York.

SAAM II

* A general purpose kinetic analysis software tool

* Developed under the aegis of a Resource Facility grant from NIH/NCRR

* Available from the SAAM Institute:

  http://www.saam.com

Moments

* Moments play a key role in estimating pharmacokinetic parameters via noncompart-mental models.
* Modern use: Yamaoka, K et al. Statistical moments in pharmacokinetics. J. Pharma. Biopharm. 1978;6:547
* Initial use: Developed in late 1930's

Moments

$$S_0 = \int_0^\infty C(t)dt = AUC$$

$$S_1 = \int_0^\infty t \cdot C(t)dt = AUMC$$